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PENICILLIN OXIDES

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EXCEPT for the early preparation of methyl and benzyl benzylpenicillinate sulphone and sulphoxide,[1] and the utilization of permanganate oxidation as an analytical tool during the penicillin syntheses of Sheehan et al.[2], this group of compounds has attracted only little attention. The oxides of free penicillins have not been investigated, and to fill this gap, the following compounds have been prepared and tested for their antibiotic activity:

I	$C_{18}H_{19}N_3O_5S$	cyanomethyl benzylpenicillinate sulphoxide
II	$C_{18}H_{19}N_3O_6S$	cyanomethyl benzylpenicillinate sulphone
III	$C_{18}H_{19}N_3O_6S$	cyanomethyl phenoxymethylpenicillinate sulphoxide
IV	$C_{18}H_{19}N_3O_7S$	cyanomethyl phenoxymethylpenicillinate sulphone
V	$C_{16}H_{18}N_2O_5S$	benzylpenicillin sulphoxide
VI	$C_{16}H_{18}N_2O_6S$	benzylpenicillin sulphone
VII	$C_{16}H_{18}N_2O_6S$	phenoxymethylpenicillin sulphoxide
VIII	$C_{16}H_{18}N_2O_7S$	phenoxymethylpenicillin sulphone
IX	$C_{16}H_{19}N_3O_5S$	phenoxymethylpenicillinamide sulphoxide
X	$C_{16}H_{19}N_3O_6S$	phenoxymethylpenicillinamide sulphone
XI		phenoxymethylpenicillin. (Standard)
XII		benzylpenicillin. (Standard)

1a Chemistry of Penicillin pp. 152 ff, 187. Princeton University Press (1949); b C.J. Cavallito and J.H. Harley, J. Org. Chem. 15, 815 (1950).

2 J.C. Sheehan and P.A. Cruikshank, J. Amer. Chem. Soc. 78, 3680, 3683 (1956); J.C. Sheehan, K.R. Henery-Logan and D.A. Johnsons, Ibid. 75, 3293 (1953).

TABLE 1

Compound	Yield	Mp.	Solvent	Analyses: Found (Calc.)				pK	pK_2'	Remarks
				C	H	N	S			
I	42	100 (d)	$CHCl_3$-ether	55.69 (55.50	5.04 4.92	10.56 10.79	8.05 8.22)			
II	68	159.5 (d)	$CHCl_3$-ether	53.36 (53.33	4.76 4.73	10.36 10.37	7.88 7.91)			
III	62	153.5-154(d)	acetone-H_2O	53.26 (53.33	4.77 4.73	10.22 10.37	7.81 7.91)			
IV	40	126.5-127	acetone H_2O	49.28 (49.20	4.55 4.82	9.54 9.56	7.35 7.30)			1 H_2O:4.86 (4.7)
V	35	126 (d)	AcOEt	54.63 (54.85	5.14 5.18	7.88 8.00	9.19 9.15)	3.5	6.7	
VI	82	128 (d)	AcOEt	51.89 (51.81	5.05 5.03	7.40 7.55	8.68 8.65)	3.4	6.4	1/4 H_2O:1.13 (1.2)
VII	44	159 (d)	acetone-H_2O	51.01 (51.23	5.10 5.10	7.38 7.47	8.63 8.56)	3.7	6.6	1/2 H_2O:2.96 (2.47)
VIII	74	135-136	acetone-H_2O	48.09 (48.00	5.00 5.04	6.94 7.00	8.01 8.00)	3.2	6.3	1 H_2O:5.7 (4.7)
IX	34	204-205 (d)	AcOH-H_2O	52.39 (52.60	5.28 5.34	11.10 11.50	8.62 8.79)			
X	46	192-193 (d)	AcOH-H_2O	50.16 (50.39	5.12 5.02	10.82 11.02	8.23 8.42)			
XI								3.9	5.4	

pK determined in 50 per cent aqueous ethanol, pK_2' in water.
Microanalyses by G. Cornali.

TABLE 2

Concentration Required for 50 per cent Inhibition

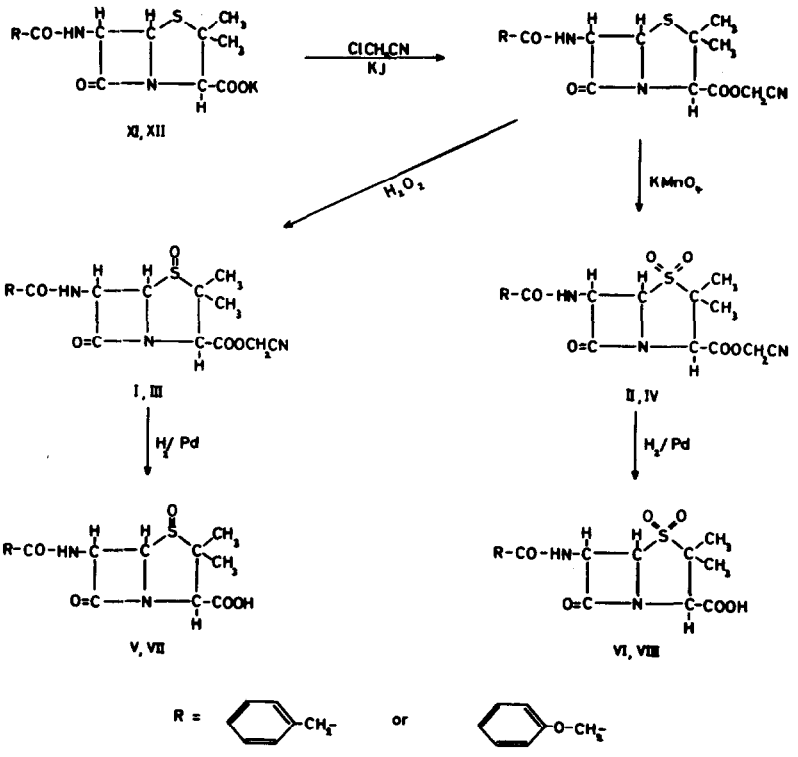
μg/ml

	Staph. aureus A	Staph. aureus B	Sarcina lutea	Bac. subtilis	E.coli	Salm. typhi-murium	Diploc. pneumo-niae	Strep. pyogenes
I	1.6	16	1.3	1.1	>100	>100	1.5	1.3
II	2.5	34	0.16	5.0	>100	>100	7.4	5.0
III	2.1	11	2.3	3.4	>100	>100	5.0	2.5
IV	13	29	2.0	9.6	>100	>100	7.4	7.9
V	2.3	16	1.6	1.6	>100	>100	1.6	0.85
VI	1.1	16	0.12	1.7	>100	>100	3.4	2.0
VII	2.2	15	1.3	3.7	>100	>100	3.3	1.5
VIII	3.2	18	1.0	4.5	>100	>100	4.7	4.0
IX	63	100	59	93	>100	>100	74	40
X	>100	>100	>100	>100	>100	>100	>100	>100
XI	0.009	1.3	0.005	0.003	93	47	0.019	0.006
XII	0.009	3.5	0.002	0.004	30	1.9	0.011	0.005

Serial dilution assay method using meat infusion broth, 5 per cent horse serum was present in test medium with *Diplococcus pneumoniae* and *Streptococcus pyogenes*. Inoculum: 10^4 cells/ml.

Staph.aureus A: Penicillin sensitive strain. *Staph.aureus* B: Penicillinase producing strain.

The physical data are summarized in Table 1, and the results of the bacteriological tests are listed in Table 2.



The general procedure of preparation consisted in transforming the penicillins into their cyanomethyl esters, according to the method employed to amino acids by Schwyzer et al.[3], followed by oxidation at room temperature in acetic acid solution. Oxidation with excess hydrogen peroxide produced the sulphoxides, while oxidation with potassium permanganate led to the sulphones. The phenoxymethylpenicillinamide was oxidized in the

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[3] R. Schwyzer, B. Iselin and M. Feurer, Helv. Chim. Acta 38, 69 (1955); R. Schwyzer, M. Feurer, B. Iselin and H. Kagi, Ibid. 38, 80 (1955).

[4] L.J. Bellamy, The Infrared Spectra of Complex Molecules (2nd. Ed.) p. 350. Methnen, London (1958).

same way.

Cyanomethyl esters are cleaved by catalytic hydrogenation, producing the free acids and acetonitrile or its hydrogenation products. When hydrogenated on a commercial Pd/C-catalyst in the presence of water, 2 moles of hydrogen are consumed. In the reaction mixture, the presence of acetaldehyde is demonstrated by paper chromatography of its 2,4-dinitro-phenylhydrazone. Further details concerning this reaction will be published later.

The penicillin oxides are slightly stronger acids than the corresponding penicillin (pK in Table 1). They are cleaved by B.cereus penicillinase a little faster than the penicillins. The acid strength of the α-carboxyl group formed by this process, shows considerable deviations from what is normally found in penicilloic acids (pK_2' in Table 1).

In the infra-red spectra in KBr of the sulphoxides, the carbonyl band originating from the β-lactam ring is displaced from its normal position at 1775 cm^{-1} to 1785 cm^{-1}. In the sulphones, this band is found in the region 1800-1810 cm^{-1}, an increased strain obviously being introduced in the four-membered ring. The absorption bands described in the literature[4] as being typical for sulphoxides and sulphones, are found at the normal position.

The compound melting at 254°C, obtained by Sykes and Todd[1] from alkaline saponification of methyl benzylpenicillinate sulphoxide, does not correspond to the compound described in this paper (V), the structure of which has been verified through oxidation of the intermediate cyanomethyl ester (I) to the corresponding sulphone (II), and esterification with diazomethane. The identity of its methyl ester with methyl benzylpenicillinate sulphoxide has been demonstrated by mixed melting point determination and infra-red spectra.